Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis

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Publication data
Submitted 30 May 2013
First decision 20 June 2013
Resubmitted 18 July 2013
Accepted 19 July 2013
EV Pub Online 19 August 2013

SUMMARY

Background
Psychotherapy is not routinely recommended for in ulcerative colitis (UC). Gut-directed hypnotherapy (HYP) has been linked to improved function in the gastrointestinal tract and may operate through immune-mediated pathways in chronic diseases.

Aims
To determine the feasibility and acceptability of HYP and estimate the impact of HYP on clinical remission status over a 1-year period in patients with an historical flare rate of 1.3 times per year.

Methods
A total of 54 patients were randomised at a single site to seven sessions of gut-directed HYP ($n = 26$) or attention control (CON; $n = 29$) and followed for 1 year. The primary outcome was the proportion of participants in each condition that had remained clinically asymptomatic (clinical remission) through 52 weeks post treatment.

Results
One-way analysis of variance comparing HYP and CON subjects on number of days to clinical relapse favoured the HYP condition [$F = 4.8$ (1, 48), $P = 0.03$] by 78 days. Chi-squared analysis comparing the groups on proportion maintaining remission at 1 year was also significant [$\chi^2(1) = 3.9$, $P = 0.04$], with 68% of HYP and 40% of CON patients maintaining remission for 1 year. There were no significant differences between groups over time in quality of life, medication adherence, perceived stress or psychological factors.

Conclusion
This is the first prospective study that has demonstrated a significant effect of a psychological intervention on prolonging clinical remission in patients with quiescent ulcerative colitis (Clinical Trial # NCT00798642).

Aliment Pharmacol Ther 2013; **38**: 761–771

doi:10.1111/apt.12449

INTRODUCTION

Ulcerative colitis (UC) affects approximately 220 per 100 000 patients in the United States[1, 2] and is associated with painful and unpredictable symptoms, undesirable psychosocial consequences[3] and disability, particularly during periods of disease flare.[4–7] Medical treatment is focused on prolonging remission and reducing exposure to environmental triggers of flare.[8] Psychosocial research in UC has been limited to survey studies characterising co-morbid anxiety or depression in the setting of disease[9] or cross-sectional studies linking stressful experiences to the onset of disease flares.[10, 11] However, the prevalence of psychological disorders in patients with UC mirrors that of the general population, particularly during quiescent disease states,[12, 13] and thus psychotherapy is not routinely recommended.[14]

Hypnotherapy (*HYP*), one of the first psychological therapies to be implemented in medical populations, has been linked to positive outcomes in a number of chronic diseases such as cancer,[15–17] rheumatoid arthritis,[18] HIV,[19, 20] fibromyalgia[21, 22] and chronic pain.[23, 24] Mechanistic studies suggest that HYP can have positive effects on immune parameters, with data supporting the effects of HYP on T-cell expression of interferon-gamma and interleukin-2,[25] increases in secretory immunoglobulin-A and neutrophil adherence,[26] and reductions in inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein and leucocyte activity.[18] HYP used in in-patient medical settings has been associated with shorter length of hospital stays, decreased need for pain medication,[27, 28] more rapid recovery from surgery[29] and faster wound healing.[30–32]

Gut-directed HYP is a form of medical hypnosis that draws upon metaphors and delivers posthypnotic suggestions specific to the improved health and function of the gastrointestinal tract. HYP has demonstrated efficacy in several gastrointestinal disorders (see Palsson[33] for a review), with treatment gains maintained up to 5 years.[34] Gut-directed HYP is well-tolerated and effective in irritable bowel syndrome,[34–36] functional dyspepsia,[37, 38] non-cardiac chest pain,[39] delayed gastric emptying[40] and relapse prevention for duodenal ulcer.[41]

Limited data are available on the use of gut-directed HYP in inflammatory bowel diseases, with most research in this area limited to small, uncontrolled case series.[42–46] One particularly compelling study demonstrated that patients with active UC who underwent *a single session* of gut-directed HYP reduced mucosal release of substance P, histamine, and interleukin-13 and serum levels of interleukin-6,[46] suggesting that HYP could have a disease-modifying impact on UC. We have previously reported on the preliminary findings from the *Ulcerative Colitis Relapse Prevention Trial* (UCRPT), an NIH-funded randomised controlled trial comparing gut-directed HYP to a time and attention CON group in quiescent UC in which a seven-session gut-directed HYP programme demonstrated improvement in health-related quality of life, including reduction in bowel and systemic UC symptoms (IBDQ, Inflammatory Bowel Disease Questionnaire) and increased disease-specific self-efficacy immediately post treatment and at 3-month follow-up.[47]

Ulcerative Colitis Relapse Prevention Trial completed data acquisition in April 2012 and we now report the results of our primary scientific question – can participation in a brief gut-directed HYP programme prolong clinical remission among patients with quiescent UC? Our hypothesis was that HYP would be superior to CON on two endpoints – (i) The proportion of patients at 52 weeks who were still clinically asymptomatic and (ii) number of days to first relapse.

MATERIALS AND METHODS

Study design

Ulcerative Colitis Relapse Prevention Trial was a prospective, single-site randomised clinical trial comparing gut-directed HYP against an active CON condition on the primary outcome variable, which was the proportion of UC patients who remained clinically asymptomatic (no rectal bleeding, no diarrhoea/urgency or requirements to increase medication) through 1-year follow-up. Repeated assessments of disease status (patient and physician), self-efficacy and quality of life were administered at baseline, 2 weeks post treatment, 20 weeks, 36 weeks and 52 weeks post treatment. This clinical trial was registered with www.clinical trials.gov/NCT00798642.

Participants

Male and female patients (ages 18–70), who were in remission, with endoscopy confirmed mild or moderately severe UC were invited to participate. Remission at the time of enrolment was operationally defined by a Mayo Score <2 with no subscale >1, and no rectal bleeding in last 2 weeks. We included only those patients who had a self-reported flare rate of >1 per year and a documented disease flare within the past 1.5 years to enhance the opportunity to observe differences between groups over the course of a 1-year trial. As such, we expected to see

primarily left-sided UC and some pancolitis with significant fewer patients with proctitis qualifying. Patients were required to be on a stable dose of maintenance medication [i.e. mesalazine (mesalamine) or sulfasalazine] for at least 1 month prior to enrolment and could not have taken oral steroids within the past 30 days or topical steroids within the past 7 days. Exclusion criteria included any markers of active disease, a history of severe/fulminant UC and other gastrointestinal disorders that could explain symptoms (e.g. Crohn's disease, indeterminate colitis, short-bowel syndrome, renal/hepatic disease, *Clostridium difficile* infection, irritable bowel syndrome), pregnancy or intention to become pregnant in the next year, smoking cessation within the past 30 days, a prior history with HYP as well as any of the common contraindications for HYP.[48] We based sample size calculations on our previous research in this area – 50 participants spread across two conditions is minimally acceptable (80% power) to detect an OR of 3.8.[47, 49]

Interventions

Both interventions were standardised and conducted on an individual, out-patient basis at a tertiary clinic in an academic medical centre. Gut-directed HYP is a seven-session standardised treatment protocol delivered by one of two trained health psychologists (LK, JLK) in weekly, 40-min sessions (Table 1 for sample hypnotic suggestion). Sessions were fully scripted to ensure uniformity across therapists. Patients were provided a self-hypnosis audio recording to practice outside of clinic five times per week during the study and then as they chose through follow-up.[47] The CON condition consisted of nondirective discussion on UC and 'the mind-body connection' with a separate postdoctoral fellow (MK). The therapist avoided any in-depth discussions of HYP or relaxation techniques to ensure difference from the experimental condition. Notably, the CON treatment was not inert – participants were able to ask questions around disease self-management of their therapist, and the therapist would point participants towards up-to-date information on behavioural self-management of IBD without directly encouraging behaviour change. This treatment was previously validated as a credible intervention that controlled for time and clinical attention. Hypnotherapists were randomised on a 2:1 ratio (JLK:LK). Randomisation allocation software was provided by the statistician (ZM) and the study coordinator enrolled and assigned participants to treatment. While blinding of the therapists or participants to the intervention was not possible, participants were blinded to study hypothesis and gastroenterologists were blinded to the treatment the participant's received (HYP or CON). Participants were told that the goal of the study was to determine if behavioural therapies are an effective complementary therapy for IBD and that they would be assigned to one of two therapies: gut-directed HYP or a mind-body therapy aimed at identifying the impact of UC on the psyche and vice versa.

To ensure that participants were blinded to hypothesis, we administered the 10 point Expectancy and Credibility Questionnaire (1 not credible, 10 completely credible) after session 1. The mean score for the HYP group was 7.5 (0.9; 6–9) and the experimental group was 7.1 (1.5; 5–9) demonstrating that each therapy was presented in an engaging and credible manner. We used separate therapists for the two conditions to reduce the effect of therapist allegiance, or the tendency for a therapist to unknowingly 'water down' a treatment they do not necessarily believe is effective, on outcome.[50] To further reduce the potential bias of not being able to blind participants or providers, all follow-up assessments were done online immediately prior to the patient's 'booster session' with the therapist. We also asked the patients not to share with their physicians the type of treatment they received until the end of the trial, so as not to influence expectancy.

Measurement: disease state

The primary outcome measure was the proportion of participants in each treatment group that were still in remission at 52 weeks post treatment. We used several subjective markers of flare given the absence of endoscopy.

Baseline sociodemographic and clinical information. Participants were asked to report several demographic and illness-related variables including disease duration, medication regimen, smoking, complementary and alternative medicine use and medical history.

Daily symptom diaries. Participants completed an online time and date stamped standard symptom diary daily using a secure, password protected website during the 2-week baseline period and throughout the treatment. The diaries asked patients to report on the presence and severity of rectal bleeding [referring to the most severe episode of the day on a scale of 0 (mild) to 3 (severe)], the number of stools during the day and the presence and severity of abdominal pain or discomfort (same scale 0–3) and general well-being [0 (generally well) to 3 (poor)]. The diary was also re-assigned in 2-week periods prior to each repeated assessment interval to confirm remission status.

Table 1 | Example posthypnotic suggestion from trial

As you sit and relax like that, and allow your whole body to be at ease, something powerful and healthy and positive is beginning to happen inside you. A powerful healing wave of change is spreading deep inside your body, focusing especially on your intestinal tract to make it healthier and more resistant to stress and inflammation … much less sensitive to stress and inflammation. Perhaps you can picture this in your mind now … maybe like a wave of medication that spreads from your stomach all the way through your intestines, coating your intestines with a strong protective coating… a … coating … that … prevents … bacteria and toxins … from … leaking … into … the … intestinal … wall … and … causing inflammation … a coating that also allows any ulcerations or wounds there might be in your intestines to heal quickly and naturally. The coating can replace any spots of unhealthy intestinal lining with a healthy, pink, smooth lining that works perfectly, effortlessly resisting anything that might try to damage it in the future. See if you can picture this now – picture the bacteria and toxins bouncing harmlessly off this strong protective coating that now covers your intestines … nothing can get in anywhere, there is no effect of these toxins on your intestinal walls, the coating is so strong that bacteria and toxins are completely unable to cause any trouble inside your intestinal tract
Or maybe you can visualise this positive healthy change in your mind as a wave of light spreading through your intestines, a bright healing light that illuminates all the areas where you have tended to have the most difficulty, allowing those areas to restore themselves to a healthier state, a healing light that spreads through your entire intestines and heals the areas where you've experienced bleeding, inflammation, pain or discomfort, and gives your whole intestinal tract greater power to resist all disease and inflammation in the future. Your whole intestinal tract is becoming more and more resistant to all disease and inflammation – more and more able to stay healthy and function perfectly no matter what happens inside you or in your life … perfectly healthy no matter what happens inside you or in your life
Perhaps you can also feel this powerful healthy wave of change that is spreading through your intestines … perhaps it feels like a wave of soothing comfort, that calms down any irritation and inflammation, calming and soothing your intestines, restoring health and making them more and more resistant to future irritation and inflammation … giving your intestines the strength and natural self-healing power that will protect you from things that can cause your symptoms to flare. And it probably also feels like comfort is flowing all through your intestines, making you more and more immune to discomfort in your intestines, causing a lasting protection against discomfort … of course, still letting healthy and pleasant sensations through in your intestines, but numbing and neutralizing all discomfort
Whatever this process of change towards better health inside you feels like, or looks like in your mind's eye, it is a powerful process of improved health and increased resistance to any illness and disease that is happening inside your body right now … and it will continue to happen steadily after you wake up from this state in a little while – causing a long-lasting improvement in your health and well-being … making your intestines healthier from this day on, more and more healthy every day … making it easier from day to day and week to week to keep your body in remission, like it is now. You, with the power of your mind and the skills you will learn in this program, will become more and more confident in your ability to maintain your remission and your health
Even when you are experiencing stress … and even though you may be exposed to toxins or bacteria or anything else that have caused your symptoms to flare in the past, you'll be surprised and pleased to find that you are no longer affected in the same way. You are protected more and more from anything that can cause disease in your colon

Flare worksheet. Participants were instructed to complete this form at the first sign of a flare regardless of whether they were currently in one of the 2-week assessment intervals for UCRPT. The form was accessible online and asked participants to identify the date they first noticed symptoms, note the presence and frequency of rectal bleeding, average number of bowel movements per day since the start of flare, average rating of abdominal pain since the start of flare, general well-being and free text describing the situation. When completed, an alert was triggered to the study coordinator who was able to follow-up for additional details.

Modified Mayo score. The Mayo Scoring System for the Assessment of UC activity is a 12-point scale that reflects the physician's clinical opinion of disease activity at each assessment interval. It was modified in this Phase I/II a study to exclude endoscopy results. This decision was based on factor analysis, which revealed that other items included in disease activity indices (rectal bleeding, stool frequency/urgency) made the histological findings obtained on endoscopy redundant, with endoscopy accounting for less than 1% of the variance in predicting disease activity scores.[51]

Inflammatory Bowel Disease Questionnaire[52]*.* Participants completed the 32-item version of the well-validated questionnaire to assess disease severity and quality of life in IBD, yielding four subscale scores: bowel health, systemic health, emotional functioning and social functioning.

Morisky Medication Adherence Scale[53]*.* Non-adherence to medication was assessed with a validated, 4-item

questionnaire and allowed us to track adherence in the study to control for the effects of adherence to maintenance medications on relapse.

Measurement: psychological questionnaires

Psychiatric comorbidity was assessed during the intake interview and participants with a psychiatric diagnosis (e.g. depression, bipolar disorder, panic disorder) were not included in this trial to maintain as much homogeneity as possible and reduce the possibility that the treatment worked through change in psychiatric symptoms.

Inflammatory Bowel Disease Self-efficacy Scale. Drawn from social-cognitive theory, self-efficacy is an individual's personal beliefs about their ability to engage in a certain behaviour/set of behaviours and has been linked to healthy outcomes in a host of chronic diseases. Disease-specific self-efficacy reflects a person's individual belief in his/her ability to manage IBD. Participants completed a 29-item validated disease-specific self-efficacy measure[54] with four subscales: managing stress and emotions, managing medical care, managing symptoms and disease, and maintaining remission.

Perceived Stress Questionnaire-Recent[55]*.* The Perceived Stress Questionnaire (PSQ)-Recent is a 30-item validated measure of stress in the past month across seven factors: harassment, overload, irritability, lack of joy, fatigue, worries and tension. Items are rated on a 4-point Likert scale from 'almost never' to 'usually.' Higher scores suggest greater perceived stress. Norms have been previously reported in IBD.[56]

Short Form 12 Health Survey Version 2[57]*.* The Short Form 12 Health Survey Version 2 (SF-12v2) includes 12 items from the Short-Form 36 Health Survey[58] and yields a physical and mental composite score. Lower scores correspond with poorer general health-related quality of life.

Determination of flare

Conservative estimates of flare occurrences were used. Patients were considered to have had a disease flare if *any* of the following were met: (i) patient completed the flare worksheet (n = 15); (ii) Modified Mayo Score >2 or subscale was >1 at the time of an assessment or self-reported flare (n = 10); (iii) patient self-reported a flare as rectal bleeding >2 days with no other symptoms between assessment periods (n = 5); or (iv) a patient's therapy was escalated to include oral or topical steroids at any point in the 12 months or a new class of medications was added (n = 8). Once a flare occurred, we recorded the date it was first reported/described to quantify the total number of days between study enrolment and time of flare. If a flare was not reported during the 12-month follow-up period and if we were unable to quantify time to the first flare, we recorded 366 days (1 year + 1 day) to flare (censored).

Maintenance of remission

We defined continued clinical remission at 52 weeks as the absence of flare (defined above) during the 1-year follow-up phase. Although there has been recent emphasis on the use of mucosal healing as the 'gold standard' determinant of remission, the study was designed during a period of time where patient-centred reports of clinical remission were of similar utility to endoscopic indices.[51, 59] Indeed, Higgins *et al.* suggested that unless a patient considers him/herself to be in remission, s/he is still likely to experience impairment, poor quality of life and high health use. Thus, the participant or his/her physician could not have reported a flare, defined above, at any of the previous follow-ups, or during the interval between week 36 and week 52. Participants were categorised at the 52-week follow-up according to the primary outcome variable: continued remission at week 52 (yes/no).

Statistical analysis

Statistical analyses were completed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Analysis of variance (ANOVA) and chi-squared tests were performed on baseline demographic and disease variables. There were no dropouts during active treatment in either condition, so intent-to-treat procedures were unnecessary. When possible, a worst case carried forward approach was employed for missing data. For example, if the patient did not have data at 1 year, they were assumed to have flared during the 52-week trial period. This approach left us with three participants whose data were too unreliable to include in the analysis and one participant who withdrew consent. A Cox proportional hazards model was used to assess differences in days to flare for subjects in HYP vs. CON. A one-way ANOVA test was performed to determine differences between the two groups on number of days to flare. Chi-squared test was used to evaluate differences between groups in the proportion of individuals who had flared by 1 year. Multivariate analyses of variance were performed to determine changes in psychological questionnaire data

over time (baseline, post treatment, 20 weeks, 36 weeks, 52 weeks).

Ethical considerations

The study was approved by the Institutional Review Board of Northwestern University. All co-authors had access to the study data and have reviewed and approved the final manuscript.

RESULTS

Participants were recruited over a 3-year period, from March 2008 to February 2011. There were no adverse effects in either treatment condition. See Figure 1 for CONSORT-NP statement. Of the 234 patients assessed for eligibility, 54 were randomised. Twenty participants were excluded from the 234 because of a contraindication to HYP (10 for objection to hypnosis for religious purposes, eight for unresolved trauma histories, two for history of mania/psychosis), another 20 were excluded for refusal to be randomised and 90 were excluded due to active disease, steroid use, smoking or other medical exclusion criteria. Four patients were excluded because of psychiatric disorder. Forty-eight patients (90%) had left-sided colitis of mild-to-moderate severity and six had pancolitis. All patients were in clinical remission at the time of enrolment.

Fifty patients (93%) were considered at 1-year follow-up (25 HYP, 25 CON). There were no differences between patients who followed up vs. failed to follow-up on demographic or clinical variables. The mean age of the sample was 38 years (range 18–65) with average disease duration of 9.5 years (range 1.5–35 years).

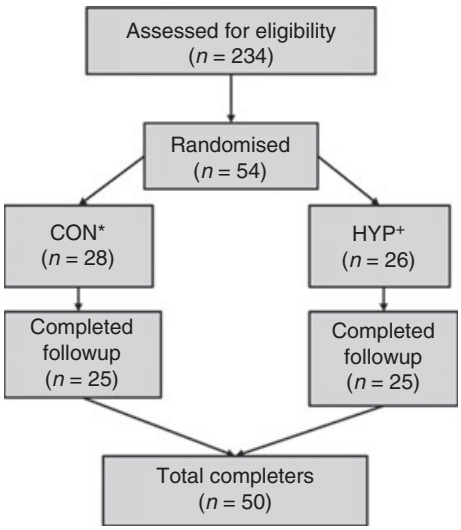

Figure 1 | CONSORT table for UCRPT. *One dropout from CON during active treatment, three dropouts in CON all occurred before 3-month follow-up. +One withdrew consent from HYP after active treatment (before 3-month follow-up).

Participants were 54% female, 86% white, non-Hispanic, 56% married and 75% with a college degree. One third reported a prior history of smoking, but no participants had smoked within the last 2 years. Sixteen per cent reported a positive family history of IBD. Seventy per cent endorsed 5ASA use and 18% reported current azathiopurine use. None of the patients was currently using a biological agent and 15% had a history of azathiopurine use. Only two participants reported no maintenance medication use. Sixty-four per cent reported a history of oral steroid use in the last 1.5 years. Participants reported an average of 1.29 flares per year (range 1–5) with an average duration of flare of 6.3 weeks (s.d. = 5.4), (range 1–24). The median number of days since last flare was 100 (19, 55–144). Baseline symptom diaries suggested that participants, who were all in remission, had an average of three bowel movements per day, mild daily abdominal pain/discomfort and excellent-to-good well-being (Table 2).

Overall baseline IBDQ score was 191 (s.d. = 19.8), reinforcing remission status and a good disease-specific quality of life estimate.

Remission status by group

A one-way ANOVA comparing HYP and CON on number of days to relapse favoured the HYP condition [$F = 4.8$ (1, 48), $P = 0.03$] by 78 days. Chi-squared analysis comparing the two groups on proportion who maintained remission at 1 year was also significant [χ^2 (1) = 3.9, $P = 0.04$] with 68% of HYP patients and 40% of CON patients maintaining remission for 1 year (Table 3). A Cox proportional hazards model was used to assess differences in days to flare for subjects in HYP vs. CON. Overall, the risk of flare was estimated to be 2.11 times greater in the CON vs. HYP; however, this result was not statistically significant (Wald chi-square = 2.87, $P = 0.090$).

Twenty-three patients flared during the study. There was one flare in a CON participant at 3-month follow-up. By 6-month follow-up, 10 CON and 5 HYP had flared, and by 12-month follow-up, 15 CON and 8 HYP had flared. Of those patients who flared, 15/23 (5 HYP, 10 CON) reported it via the flare worksheet between assessment intervals and 10 of these were also confirmed by physician's Modified Mayo Score (2 HYP, 8 CON). The additional eight participants who flared but did not

Table 2 | Baseline and demographic characteristics of patients by condition

Variable	Hypnotherapy (n = 25)	Attention control (n = 25)
Gender	56% female (n = 14)	52% female (n = 13)
Race	84% white (n = 21)	88% white (n = 22)
Ethnicity	4% non-white Hispanic (n = 1)	4% non-white Hispanic (n = 1)
Marital status	48% married/life partner (n = 12)	64% married/life partner (n = 16)
Education	86% college degree or higher (n = 19)	68% college degree or higher (n = 17)
	Mean (s.d.)	Mean (s.d.)
Age	38.7 (11.8)	38.8 (12.1)
Disease duration (years)	9.38 (7.95)	9.96 (6.73)
Disease extent	84% (n = 21) left-sided colitis, 16% (n = 4) pancolitis	88% (n = 22) left-sided colitis, 12% (n = 3) pancolitis
No. of BM/day	3.1 (0.88)	3.3 (1.4)
Abdominal pain	1.3 (0.43)	1.3 (0.46)
Well-being	1.21 (0.37)	1.2 (0.54)
No. of flares per year	1.29 (0.46)	1.29 (0.46)
Days since last flare	102.6 (20.8, 60–144)	99.2 (18.9, 55–136)
+ 5ASA use (current)	18 (72%)	17 (68%)
+ Azathioprine/mercaptopurine use (current)	4 (16%)	5 (20%)
Duration of last flare (weeks)	6.1 (4.9, 1–16)	6.6 (6.0, 0.1–24)
+ History of smoking	8(32%)	7 (28%)
+ Family history of IBD	5 (20%)	3 (12%)

All patients were in remission at the time of enrolment.

No differences between groups on any variables.

Table 3 | Changes in primary outcome measures at 1 year

Variable	Hypnotherapy (n = 25) Mean (s.d.)	Attention control (n = 25) Mean (s.d.)	Test statistic
Days to relapse	359.4 (145.9)	281.8 (100.5)	t = 2.1 (1, 48), P = 0.03
Proportion still in remission at 1 year	17 (68%)	10 (40%)	$\chi^2(1)$ = 3.9, P = 0.04
IBDQ	↑2.3 (24.1)	↓7.9 (20.7)	t (1,48) = 0.24, P = ns

IBDQ, Inflammatory Bowel Disease Questionnaire.

complete a worksheet were identified through the medical record as requiring an escalation in therapeutic dose (3 HYP, 5 CON). Five/twenty-three participants who flared reported rectal bleeding >2 days as their sole indicator of flare (3 HYP, 2 CON), but were not confirmed to have flared by the medical record or physician Mayo rating. Of those patients who flared, 22% (5) were stepped up from 5ASA only to azathioprine/mercaptopurine and 30% (7) had an escalation in 5ASA use. Nineteen per cent (4) required oral steroid use at the time of flare. There was no significant difference between groups in approach to flare. We were not powered to detect impact of HYP on flare characteristics.

There were no main effects or group × time interaction effects for any of the psychological questionnaires at 1-year follow-up [F = 1.4(24, 16), P = 0.28] (Table 4).

We also monitored adherence to recommended weekly, at-home practice and at 1-year follow-up, 52% of the HYP group was practicing self-HYP at least once per week.

DISCUSSION

This is the first prospective study to our knowledge that has reported a demonstrable effect of a psychological intervention in prolonging remission in patients with quiescent UC. We found that HYP prolonged remission by a very conservative estimate of approximately 2.5 months, which is likely to be a clinically and subjectively significant benefit of the therapy considering that these patients had a preintervention annual flare rate of 1.3.

There are several strengths to this study. Participants were selected based on a flare rate of >1 per year and

Table 4 | Changes in psychological variables over time: (a) hypnotherapy (n = 25) and (b) attention control (n = 25) groups

Variable	Baseline	Post Tx	Week 20	Week 36	Week 52
(a)					
IBDQ perceived stress self -efficacy SF12 MCS	187.5 (22.4)	190.0 (22.5)	189.7 (25.2)	184.1 (24.7)	185.2 (26.0)
SF12 PCS	36.4 (14.4)	33.1 (18.1)	33.1 (18.1)	35.6 (17.4)	34.8 (16.0)
	212.8 (48.5)	221.5 (48.6)	221.8 (54.6)	225.7 (43.6)	218.7 (56.8)
	44.9 (10.9)	48.4 (11.1)	48.0 (9.4)	45.8 (11.3)	45.6 (12.2)
	52.3 (6.8)	53.6 (4.6)	53.2 (4.8)	54.3 (5.3)	53.8 (4.9)
(b)					
IBDQ perceived stress self -efficacy SF12 MCS	181.8 (20.7)	186.7 (22.2)	188.8 (18.8)	188.9 (20.9)	189.7 (20.6)
SF12 PCS	37.2 (14.3)	34.3 (12.3)	33.5 (12.3)	31.7 (14.2)	30.7 (12.1)
	203.4 (40.6)	204.7 (43.4)	208.8 (38.4)	208.6 (39.2)	216.2 (38.1)
	44.6 (9.5)	48.3 (5.9)	44.7 (8.7)	46.2 (8.2)	46.8 (7.7)
	52.3 (6.8)	52.6 (8.2)	53.4 (8.2)	53.5 (8.4)	53.0 (9.2)

Values represent mean of s.d.

were 'primed' for flare in that eligibility criteria required a documented disease flare within the past 18 months, making it more likely that they would flare during the course of the 1-year follow-up period. However, the average flare rate still fell within 1–2 per year. Thus, it is significant that 68% of the HYP group did not flare during the year post treatment, contrary to the 40% seen in the time-attention CON group. It is also important to note that the CON group in this study was a one-on-one verbal intervention provided by a doctoral level therapist, not simply routine care.

Comparing our intervention to wait-list (treatment as usual), while less rigorous, would likely have yielded more stunning results. Indeed, we have previously demonstrated that there is some immediate benefit on risk of flare derived from an active placebo condition.[49] Furthermore, we did not detect a difference in treatment expectancy at baseline, suggesting that both treatments were presented with strong rationale.

That we were able to detect a difference between groups followed prospectively over 1 year with only 50 participants suggests that HYP is likely to be an effective complementary intervention in patients with mild-to-moderate UC, especially in contrast to no intervention, which is currently what patients receive in IBD centres. Furthermore, the majority of participants were practicing self-HYP on their own at 1 year, supporting its potential for sustainability and self-management therapeutic benefit even when a health psychologist is not readily available. Our results mirror IBD patient's positive attitudes about the use of complementary and alternative therapies in IBD.[60] Finally, the fact that the HYP followed a standardised scripted protocol means that the same precise therapeutic components were delivered to all patients, and also that this intervention can easily be replicated, further tested and applied in clinical care by other groups.

Only 52% of the participants engaged in home practice of the hypnosis audio file, yet there was no relation between practice and no practice in terms of flare outcome. Previous research has shown lasting effects of gut-directed HYP (up to 7 years) on bowel symptoms, motility, abdominal pain and visceral hypersensitivity in functional gastrointestinal problems.[33, 61, 62] Mechanisms proposed for these findings include cognitive change around the meaning of symptoms, improved motility and improved pain tolerance.[62–64] Similarly, enduring effects of HYP have been attributed to learning that occurs occurring at the neurophysiological level; this has been linked to the depth of trance[65] and type and ease of suggestion[66] and may be interesting for future research. Less is known about long-term benefits of hypnosis in chronic autoimmune conditions, but it is possible that increased awareness of body processes, improved self-care after participating in a programme during remission and strengthening of the immune system more generally may explain some of the long-term effects of HYP noted in this study. Finally, recent support for the importance of brain–gut interactions in the clinical expression of IBD[67] is highly compatible with our complementary approach to treatment – to the extent that gut-directed HYP has been shown to modify brain–gut pathways and visceral hypersensitivity in functional gastrointestinal disorders such as irritable bowel syndrome,[68] it is possible that our intervention could impact IBD disease outcomes in a similar manner.

It is unlikely that patients participated in this study because of psychological distress – indeed our patient population did not evidence any clinically significant depression, anxiety or stress at the time of study entry, which is consistent with other reports of psychological characteristics of patients with quiescent UC. The IBDQ, a well-recognised index of disease-specific quality of life,[69] did not change with treatment in our group, likely because it is of limited value when patients are in remission at baseline[70]; differences in quality of life over time were not detectable, even in the group with a higher flare rate. Finally, rate of adherence to medication did not differ over time between the two groups, so adherence does not explain the difference in remission status over the course of 1 year.

We acknowledge a few important limitations to the study. First, we did not confirm flare and remission status endoscopically and instead relied on clinical symptoms, corroborated through daily symptom diaries, medical records, and patient and physician report. Inflammation has been shown to be present when clinical symptoms are absent in UC[71] and mucosal healing is gaining acceptance as an endpoint in clinical trials.[72] We wish we had been able to use faecal calprotectin as a biomarker of flare or risk to flare for this study – at the time the NIH grant was awarded, this biomarker was still quite novel and expensive and not feasible for a pilot trial. Indeed, recent data suggest that high levels of perceived stress may contribute to higher symptom burden without altering faecal calprotectin levels, underscoring the importance of both objective and subjective markers of flare.[73] We cannot draw any conclusions on the mechanism through which HYP may have prolonged remission in this study, which highlights an interesting area for future research. Secondly, our patient population may not be representative of the typical UC patient seen in clinical practice – we are a tertiary care centre with an integrated behavioural medicine and nutrition programme and therefore our patients may be more motivated to participate in this type of research. An important next step in this line of inquiry would be a multi-centre trial with a range of care settings and patient phenotypes. Finally, because the lead author served as a therapist in the HYP condition, it is possible that researcher allegiance impacted the outcome.[50] Unfortunately, at the time of the study, the lead author was also one of the few individuals qualified to provide the therapy. That said, the HYP was well-scripted and therefore it would have been difficult to impose considerable expectancy onto the individual patient. Futuremore, multi-centre trials could address this by training therapists.

If gut-directed HYP is effective in augmenting the time patients spend in clinical remission for even a portion of patients with UC, this would have marked clinical significance for the conventional management of IBD. This intervention may prove particularly useful for the large number of patients who have high rates of flare, difficulty obtaining remission, who become steroid dependen, or are otherwise resistant to maintenance medications.

SUMMARY

This study reports on an NIH-funded RCT of gut-directed HYP in quiescent UC (NCT00798642). The primary aims were to determine the feasibility and acceptability of HYP and estimate the impact of HYP on clinical remission status over a 1-year period in patients with an historical flare rate of 1.2 times per year. This is the 1-year follow-up study reporting on the impact of HYP on relapse. We found that patients receiving HYP were able to prolong clinical remission by 78 days, with 68% of HYP patients and 40% of CON patients maintaining remission for 1 year.

AUTHORSHIP

Guarantor of the article: Laurie Keefer.

Author contributions: LK contributed to the study concept and design, data acquisition, analysis and interpretation, manuscript preparation, statistical analysis, obtained funding, study oversight. TT performed the data acquisition, analysis and interpretation, manuscript preparation. JLK performed as the primary therapist, data acquisition, administrative support and manuscript revision. TAB contributed to the study concept and design, subject recruitment and retention, medical oversight. ZM contributed to the study concept and design, statistics, analysis, interpretation of data. OP contributed to the study concept and design, development and oversight of the hypnotherapy intervention, critical revision of manuscript for important intellectual content. All co-authors had access to the study data and had reviewed and approved the final manuscript.

ACKNOWLEDGEMENT

Declaration of personal interests: None.

Declaration of funding interests: This study was funded in full by National Institutes of Health, grant number R21AT0032004, clinical trial #NCT00798642. We also

thank Monika Kwiatek, PhD for her assistance with the control condition, Edward Loftus, MD for his assistance with the choice of outcome measures, Rachel Lawton for her assistance with final chart review and all of the participants for their commitment to the project.

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